REMARKS

With the entry of the above amendments, claims 1, 2, and 4-27 are pending in this application. Claims 5-16 have been withdrawn. Claims 19-27 have been added. Claims 19-21 have been added to claim a method for delivering human granulocyte colony stimulating factor. Basis for these claims are found on page 17, lines 1-29 of the specification. Claims 22-24 have been added to claim a method for delivering human parathyroid hormone. Basis for this amendment is found on page 18, lines 1-20 of the specification. Claims 24-27 have been added to claim a method for delivering human growth releasing hormone. Basis for this amendment is found on page 18, lines 22-30, and page 19, lines 1-6 of the specification. Claim 4 has been amended to indicate that the analog exhibits at least about the same "type and amount of" biological activity as the parent polypeptide agent. Basis for this amendment is found on page 8, lines 18-24 and page 13, lines 1-29 of the specification. Claim 18 has been amended to correct a grammatical error in the claim. The title of the application has also been amended as recommended by the Examiner. Applicant respectfully submits that no new matter has been added by these amendments.

The application has been objected and rejected to as follows. The title of the invention has been objected to as not being descriptive. Claim 18 has been objected to as containing a grammatical error. Claim 4 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1, 2, 4 and 17-18 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Claims 1, 2, 4 and 17-18 stand rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Claims 1, 2, 4 and 17-18 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5, 250, 022 issued to Chien et al. (hereinafter "Chien") in view of Green et al., *Pharm Res* 8:1121-1127 (hereinafter "Green") and Markussen et al., *Protein Engineering* 2:157-166, (hereinafter "Markussen"). Applicant traverses these objections/rejections for at least the reasons presented below.

Objection to the title

The Examiner has objected to the title of the application as not being descriptive. Applicant has amended the title to read "Method of Enhancing Electrotransport Polypeptide Flux by Amino Acid Substitution with Histidine" as recommended by the Examiner. Applicant respectfully requests that the objection to the title be withdrawn.

Objections to claim 18

The Examiner has objected to claim 18 as containing a grammatical error. Applicant has amended claim 18 to correct this error. Applicant respectfully requests that the Examiner withdraw the objection to claim 18.

Rejections under 35 U.S.C. § 112, second paragraph, as to indefiniteness

The Examiner rejected claim 4 under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner stated that the recitation "the same biological activity as the parent polypeptide agent" is indefinite, as it is unclear whether the term is meant to be interpreted as meaning the analog has the same type of biological activity as the parent polypeptide, or whether the analog maintains the same amount of biological activity of the parent polypeptide. Claim 4 has been amended to indicate that the analog exhibits at least about the same "type and amount of" biological activity as the parent polypeptide agent.. Basis for this amendment can be found on page 8, lines 18-24 and page 13, lines 1-29 of the specification. Given the context of the disclosure, an individual of ordinary skill in the art would understand that the analog has the same type of activity as well as the same amount of activity. Applicant respectfully requests that the Examiner withdraw the rejection to claim 4.

Rejections under 35 U.S.C. § 112, first paragraph, as to written description

The Examiner rejected claims 1, 2, 4, and 17-18 under 35 U.S.C. § 112, first paragraph, as failing to describe the subject matter of the claimed invention as to reasonably convey to one of ordinary skill in the art that the inventor had possession of the invention. Specifically, the Examiner argues that the specification teaches only one representative species of a pharmaceutical polypeptide agent (human parathyroid hormone with, glutamine at position 29 replaced with histidine) has biological activity that is maintained. The Examiner states that while the specification describes the structures of two other polypeptides (human granulocyte colony stimulating factor and human growth releasing hormone) there is no disclosure that the synthetic analogs of these peptides, as modified by the method of the present invention, maintain their biological activity. The Examiner argues that specification fails to describe any other representative species of pharmaceutical polypeptide agents that maintain biological activity, or provide any teaching of any other identifying characteristics of such polypeptides of the claimed genus.

Applicant traverses this rejection for a number of reasons.

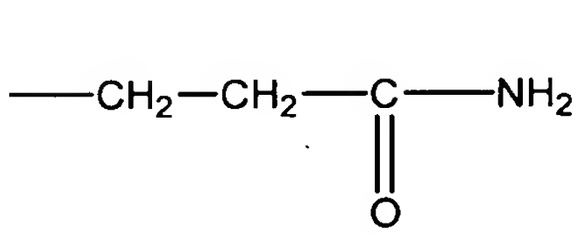
First, only claim 4 of the application contains the limitation that "the analog exhibits at least about the same type and amount of biological activity as the parent polypeptide agent." Claims 1, 2, and 17-18 do not contain this limitation. These claims should not stand rejected under the reasoning set forth by the Examiner, as the claims fail to contain the limitation the Examiner contends is not fully described in the specification.

Second, Applicant respectfully submits that the Examiner is in error in the contention that the specification fails to disclose that the polypeptides human granulocyte colony stimulating factor and human growth releasing hormone have maintained biological activity when modified by the method of the present invention. The specification indicates that for human granulocyte colony stimulating factor "substitution of one or more up to and including all of the Gln's of G-CSF with His residues produces an analog which exhibits a specific activity close to that of unmodified or parent G-CSF." (See page 13, lines 4-6 of the specification). For human growth releasing hormone, the specification indicates that "a modified h-GHRH gene can be prepared by inducing site-specific mutagenesis in the h-GHRH gene at codons specifying positions 16, 24, 30, 31 , 36 or any combination of two or more positions which preserve or increase biological activity." (See page 13, lines 22-25 of the specification).

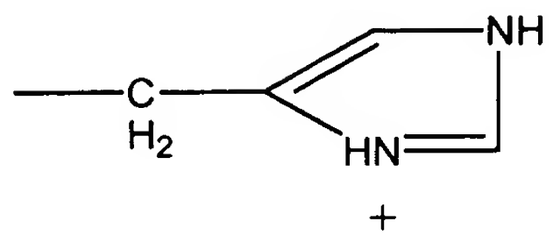
Third, the application adequately describes, to one of ordinary skill in the art, parent polypeptides that can be used as a template for the modified polypeptide analog having similar biological activity to that of the parent polypeptide. The specification indicates that all polypeptides having a molecular weight of about a few hundred daltons to about 30,000 daltons (see page 9, lines 19-21) can be utilized as a parent polypeptide in the claimed method of the invention. The specification also discloses how the modification of the parent peptide does not significantly alter the biological activity of the peptide. The specification discloses that:

> "Replacing His for Gln, Asn or Thr in accordance with the present invention is viewed as a "conservative" modification or derivatization of a polypeptide or protein. By this it is meant that the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide or protein are preserved in the analog. The preferred substitution of His for Gln is the most conservative of the three possible substitutions since the hydrogen bonding capacities, charges at pH_7, and side chain volumes of the analog so synthesized are virtually identical to the parent compound.

The side chain structures of Gln and His residues are shown below:



Gln



His

The side chains of the Gln and His residues reveal a considerable similarity in the geometries of hydrogen bonding capability, i.e., the replacement of Gln by His does not appreciably alter the hydrogen bonding capacity of the side chain. Depending on the bond angles between the planar amide group, the {1 CH2 and the *a* CH2, hydrogen bonds involving the Gin side chain can also be made by a His side chain.

> Further, the hydrophobicities of His (uncharged state) and Gln residues are very similar. See, Tanford et al., *I. Biol. Chem.,* vol. 246 (1971) 2211-2217, where the hydrophobicities of amino acid side chains in both water and various alcohols were measured, and very similar transfer free energies for His and Gln were found in moderate concentrations of dioxane." (See page 10 lines 24-31 and page 11, lines 1-10 of the specification.)

Given that the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of the parent polypeptide or protein are preserved in the modified analog of the parent polypeptide, one of ordinary skill in the art would expect that the biological activity of the analog would be similar to that of the parent polypeptide.

Applicant respectfully submits that the specification adequately demonstrates, to one of ordinary skill in the art, that the inventor had possession of the invention at the time the application was filed. Applicant respectfully requests that the Examiner withdraw the rejection to the claims on this ground.

Rejections under 35 U.S.C. § 112 first paragraph, as to enablement.

The Examiner rejected claims 1, 2, 4, and 17-18 under 35 U.S.C. § 112, first paragraph, as not being enabled for delivering, by electrotransport, any pharmaceutical polypeptide agent having any residue or optionally, Gln, Thr or Asn residues(s), replaced by His, and optionally, wherein the analog exhibits the same biological activity as the parent peptide. The Examiner contends that undue experimentation would be required given that 1) the breadth of the claims covers any pharmaceutical polypeptide agent having any Gln, Thr,

or Asn residues replaced by His, 2) the specification fails to provide adequate guidance for making an using the entire scope of the delivery methods as encompassed by the claims and 3) given the unpredictability in the art, one would recognize that there is no method for accurately and reproducibly predicting the effects of a protein's activity following amino acid mutation.

Applicant respectfully submits that the claims of the application meet all of the statutory enablement requirements of 35 U.S.C. § 112, first paragraph.

The specification clearly sets forth specific parent polypeptides of interest (page 9, lines 19-31 and page 10, lines 1-15 of the specification) and provide additional teaching as how do identify other parent polypeptides of interest, specifically those having a molecular weight of about a few hundred daltons to about 30,000 daltons (see page 9, lines 19-21). In light of such teaching, one of ordinary skill in the art could easily determine parent polypeptides that could be utilized in the present invention.

The specification also sets forth how to derive the analogs of the present invention. The various methods of synthesizing the analogs of the present invention were well known in the art at the time the application was filed. Specifically, the specification sets forth that the peptides can be synthesized by solid phase synthesis, wet chemistry methods and biotechnoligal methods. The specification points to specific articles and texts, incorporated by reference, which discloses the specific methods which one of ordinary skill in the art would be familiar with for synthesizing the analogs of interest (See page 11 lines 14-31 and page 12 lines 1-27 of the specification).

The application also sufficiently sets forth to one skilled in the art, how to use the analog of the present invention in electrotransport. The specification teaches an exemplary electrotransport device (See Fig. 1 and page 14 lines 28 to page 16, line 20) and provides specific examples of the electrotransport of human granulocyte colony stimulating factor, human parathyroid hormone and human growth releasing hormone. (See pages 17-19 of the specification).

The application also specifically discloses how the similarity of His to certain amino acid residues, suitably Gln, Thr and Asn, leads to the biological activity of the analog being similar to the parent polypeptide. As discussed above, the hydrophobicity, net charge at physiological pH, volume, and hydrogen bonding capacities of a parent polypeptide or

protein are preserved in the modified analog of the parent polypeptide as taught by the present invention. (See page 10, lines 18-20). Given this fact, one of ordinary skill in the art would expect that the biological activity of the analog would be similar to that of the parent polypeptide.

Given the disclosure of the specification, and the skill and knowledge of one of ordinary skill in the art at the time the application was filed, Applicant respectfully submits that the cited claims meet all of the statutory enablement requirements of 35 U.S.C. § 112, first paragraph. Applicant respectfully requests that the Examiner withdraw the rejections to the claims on this basis.

Rejections under 35 U.S.C. § 103(a) over Chien in view of Green and Markussen

The Examiner has rejected claims 1, 2, 4, and 17-18 under 35 U.S.C. § 103(a) as being obvious over Chien in view of Green and Markussen. Applicant respectfully submits that the Examiner has not set forth a *prima facie* case of obviousness with respect to these claims.

The Manual of Patent Examining Procedure ("MPEP") § 2142 states that:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Applicant respectfully submits that the Examiner has failed to provide any objective evidence that one of ordinary skill in the art would have been motivated to combine the three references cited as the sole basis for rejecting claims 1, 2, 4, 17, and 18, (i.e. Chien, Green, and Markussen). Furthermore, Applicant submits that neither the cited references, nor the knowledge of one of ordinary skill in the art, would have motivated such a skilled artisan to combine the references to produce the present claimed invention.

The primary reference cited by the Examiner, Chien, is directed to an iontotherapeutic device having two chambers separated by a permselective membrane. Ionizable

pharmaceuticals placed in the second, lower, chamber of the reservoir are prevented from migrating into the upper, first chamber during the iontophoretic process by the permselective membrane. Chien discloses that one of the ionized pharmaceuticals that can be delivered using the Chien device is the protein, insulin. Chien further discloses what is well known in this art, that in order for there to be an ionized insulin molecule present which is deliverable by iontophoresis, the pH of the buffer of the lower chamber must be different than the pKa of the insulin. Were the pH of the lower chamber the same as the pKa of the insulin, no iontophoretic delivery of any insulin would occur because no ionized insulin would be present.

It is well established law that patentability under 35 U.S.C. § 103 is determined in light of all the teachings of each prior art reference, considered in its entirety for all it would have taught or suggested to one of ordinary skill in the art at the time the subject invention was made. *Connell v. Sears. Roebuck & Co.*, 722 F.2d 1542, 1549 (Fed. Cir. 1993); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Bausch & Lomb. Inc. v. Barnes-Hind Hydrocurve. Inc.*, 796 F.2d 443, 448 (Fed. Cir.1986), cert. den., 484 U.S. 823, 108 S.Ct. 85 (1987). When the Chien reference is viewed as a whole, as required, one can see the reference teaches nothing even remotely related to the claimed process of this invention. Specifically, one can clearly see that Chien neither teaches nor suggests the provision of an analog of a pharmaceutical polypeptide across a body surface in either reservoir of that device, much less provision of a Histidine-substituted analog. The Chien et al. invention is a device. Methods for enhancing delivery of pharmaceuticals by iontophoresis are not even remotely of concern or interest to Chien et al.

The secondary reference, Green, relates strictly to tripeptides. The claims of the present application concern the delivery of polypeptides. The insulin delivered with the iontophoresis device of Chien is a protein, one made up of multiple polypeptides linked to one another in a complex tertiary structure having a molecular weight of over 5,700 Daltons. Green is cited as teaching anodal iontophoresis of a peptide containing histidineis enhanced at pH's where histidine is positively charged. The Examiner contends that Green provides motivation to utilize an insulin polypeptide comprising an introduced histidine as it teaches positive charges available at lower pH's result in enhanced iontophoresis transfer. This statement must be understood to relate to the tripeptides discussed by Green because tripeptide's are all that is discussed in that reference.

The Examiner's characterization of Green and the implicit invitation to combine its tripeptide disclosure with the insulin disclosure of Chien ignores statements and figures presented in Green that would discourage one from combining Green with any or all of the cited references. Specifically, Green teaches away from the adaptation of the tripeptide teachings of that reference to larger molecules, such as polypeptides, by reporting in the abstract "It appears that normalized iontophoretic flux of these anionic species is independent of lipophilicity but may be inversely related to molecular weight." Green also notes a "possible inverse dependence [of normalized anion flux] on molecular weight" as indicated in a plot of normalized flux, during cathodal iontophoresis, obtained from synthetic tripeptides wherein the variable amino acid residue was one of several different anionic amino acids. (See Green, page. 1126, col. 1, last paragraph, citing Fig. 4, p. 1124). Note that the histidine containing tripeptide was the only tripeptide delivered by anodal iontophoresis, and no similar molecular weight correlation study was reported therein. However, Applicant submits that Figure 4 and the accompanying text, cited above, teach away from the substitution of histidine into larger molecular weight molecules than tripeptides, by indicating that electrotransport flux capacity is inversely proportional to molecular weight, i.e., it decreases with increasing molecular weight. From Green, one skilled in the art would be led to believe that use of molecules larger than tripeptides would reduce electrotransport flux.

Green discloses the electrotransport characteristics of synthetic tripeptides, one of which includes a histidine residue. The tripeptides studied therein were all of the general formula Ac-Ala-X-Ala-NH(Bu^t), in which the carboxy and amino termini (both alanine residues (Ala)) were blocked to neutralize the charge of each such terminus, and the central amino acid residue (X) varied. Green reports the results of studying various physical and electrotransport characteristics of each such synthetic tripeptide, and indicates that only a tripeptide with a histidine residue exhibited enhanced electrotransport flux compared to the other tripeptides in the study. Tripeptides and polypeptides are so different from one another that one of ordinary skill in the art of iontophoresis of polypeptides, particularly proteins, would not have been motivated by the simple tripeptide study of Green to practice the method of delivery of the present invention. All the claims of the present application are directed to various aspects of a method of delivery of a "synthetic polypeptide analog" across a body surface by electrotransport (see claim 1). The same "polypeptide" language is also used throughout the present specification. Green is directed to the electrotransport characteristics of tripeptides, and specialized tripeptides at that (charge on the terminal amino

acids of the tripeptides was blocked). That reference is clearly not directed to the provision of histidine substituted analogs of polypeptides and certainly does not disclose or suggest the presently claimed invention.

The longer the polypeptide, the more likely it is to fold back on itself and form secondary or tertiary structures between the various amino acid residues in the molecule. Proteins frequently consist of at least two polypeptide molecules assembled together in a quaternary structure. The secondary, tertiary, and quaternary structure of polypeptide molecules are often closely related to the biological activity, and overall charge characteristics of the molecules or multi-molecular assemblies. The inherent complexity of polypeptide chemistry makes it nearly impossible for one of ordinary skill in the art to extrapolate from the results of studies of small molecules, such as tripeptides, to determine whether results of such studies would produce similar results in polypeptides.

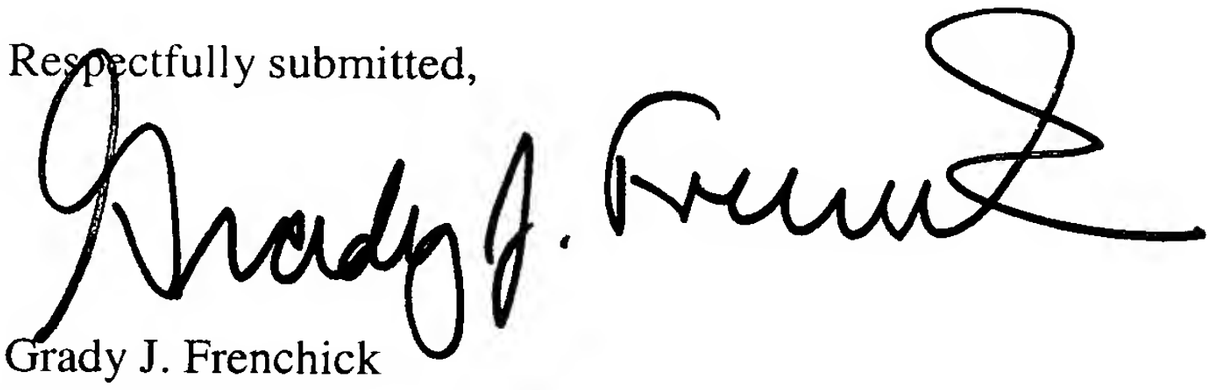
The other secondary reference cited in combination with Chien and Green as basis for rejecting claims 1, 2, 4, and 17-18 is Markussen. Markussen similarly fails to provide any teaching or suggestion which would have motivated one of ordinary skill in the art to combine that reference with the other two references to produce the present invention. Markussen merely discloses the results of a study of the stability of various analogs of insulin, including an analog produced by substituting Histidine for a particular Glutamine residue of a naturally occurring form of insulin. Markussen states that the histidine-substituted insulin analog was found to be biologically active, and more stable than other analogs studied therein. Markussen does not mention iontophoretic drug delivery. Specifically, Markussen neither teaches nor suggests that the Histidine-substituted analog of insulin described therein would have an enhanced electrotransport flux capacity, as is taught by the present disclosure. In fact, Markussen makes no mention of the electrotransport of peptides, polypeptides, or proteins of any shape or form. In other words, the combination of references Chien, Green, and Markussen have no connection which would provide a basis for one skilled in the art even to attempt to combine their teachings.

As set forth above, the Examiner has not set forth that the references provide sufficient motivation to be combined. Applicant, therefore, respectfully submits that a *prima facie* case of obviousness has not been made.

CONCLUSION

Based on the foregoing, Applicant submits that the above amendments and remarks have placed the application in condition for allowance, and a favorable action thereon is respectfully requested. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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